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10/540,086

12/28/2005

Krishna Prasad Hanumanthappa

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EXAMINER

BAUSCH, SARAE L

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/540,086	Applicant(s) HANUMANTHAPPA ET AL.	
	Examiner Sarae Bausch PhD	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 25-46 is/are pending in the application.
- 4a) Of the above claim(s) 25, 29, 30, 45 and 46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26-28 and 31-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 June 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to applicants correspondence mailed 03/26/2009. The amendment to the claims mailed 05/05/2008 has been entered.

Specification

2. The amendment to the specification mailed 03/26/2009 has been entered however this amendment is not in sequence compliance. On page 5 of the amendment, last paragraph recites M, SEQ ID No but no corresponding number, it appears as though the amendment should recite M, SEQ ID NO 3. Appropriate correction is required as the application failed to comply with requirements of 37 CFR 1.821-1.825.

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The specification on page 2 line 24 contains a hyperlink.

Election/Restrictions

4. Applicant's election with traverse of group II, SEQ ID NO 1, 2, and 7 in the reply filed on 12/07/07 and 05/05/08 is acknowledged. The traversal is on the ground(s) that Cohey et al. does not teach or suggest the claimed invention the differentiation of mycobacteria species, M. tuberculosis/M.bovis based on target gene encoding for histone like proteins such as hupB. This is not found persuasive because the claims do not require the differentiation of M. tuberculosis and M. bovis the claims are drawn to a hupB gene comprise of SEQ ID NO 8 or 7 as claimed in claim 25 (claim 45-46) and thus the sequence of SEQ ID NO 8 or 7 will inherently have the property of differentiation of M. tuberculosis and M. bovis. SEQ ID NO 7 and SEQ ID NO 8 are

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disclosed in Cohavey. Furthermore, the special technical feature of group I and II was considered to be the hupB gene of a mycobacterium species not differentiation of mycobacteria species as asserted by applicant, the hupB gene is disclosed in Cohavey thus, the technical feature linking the groups does not constitute a special technical feature and thus is not a contribution over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 24, 29-30, and 45-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/07/2007.

6. Claims 26-28, 31-44 are under examination with regard to SEQ ID NO 1-2.

Drawings

7. The drawings are acceptable.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 26-28, 31-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamerbeek et al. (J Clin Microbiol, 1997, vol 35, pp. 907-914) in view of Furugen (Microbial Pathogenesis 2001, vol. 30, pp 129-138), Hogan et al. (US Pat. 5,541,308, July 30, 1996) and Buck et al (Biotechniques (1999) 27(3):528-536).

Kamerbeek et al. teach simultaneous detection and differentiation of *M. tuberculosis* by amplification of a DR region with known interspersed spaces repeats by PCR. Kamerbeek teach amplified DNA was used directly for hybridization to differentiation different hybridization patterns to differentiate mycobacterial strains and species (see pg. 910, 1st column). Kamerbeek teaches that the DR region had five absent spaces and distinguished *M. bovis* from *M. tuberculosis* (see pg. 910, 2nd column), thus teaches differentiation consists in determining smaller size of amplified fragments. Kamerbeek teach obtaining DNA from bacterial cultures, sputum, and other clinical specimens of patients, followed by amplification of DNA and hybridization of DNA probe and detection of hybridization(see pg. 909). Kamerbeek does not teach amplification of *hupB*, primers SEQ ID NO 1, 2, probe SEQ ID NO 7, or amplified fragments of 618, 645, 291, 318, 89, 116, or 27bp.

However, Furugen et al. teach the sequence of *hupB*, MDP1, for *M. bovis* and *M. tuberculosis*. Furugen et al. teaches that there is a 9 amino acid insertion region in *M.*

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tuberculosis, which is not found in *M. bovis*, *M. leprae* or other unrelated microorganisms (see figure 6). Thus, Furugen teaches the *hupB* differentiations between *M. bovis* and *M. tuberculosis*.

Hogan et al. (herein referred to as Hogan) teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers,

"Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.

First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate T_m . The beginning and end points of the probe should be chosen so that the length and %G and %C result in a T_m about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (col. 10, lines 13-15). Oligonucleotides complementary to sequences adjacent to the probe regions were synthesized and used in the hybridization mix according to Hogan et al., U.S. Pat. No. 5,030,557, filed Nov. 24, 1987, entitled "Means and Method for Enhancing Nucleic Acid Hybridization (the "helper " patent application). Hogan

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teaches that oligonucleotide probes may be labeled by any of several well known methods such as radioisotopes, non-radioactive reporting groups, non-isotopic materials such as fluorescent molecules (col. 10, lines 45-60). Hogan teaches that probes may be labeled using a variety of labels, as described within, and may be incorporated into diagnostic kits.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states “The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2).” Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to perform the method of amplification of a region that differs in size between mycobacterial species using clinical samples and cultures of DNA as taught by

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Kamerbeek and further modify the method to include amplification of the HupB gene as Furugen teaches that hupB gene has a 9 amino acid sequence variation in mycobacterial species. Due to the teaches of Furugen that the hupB gene has a 9 amino acid sequence variation in *M. tuberculosis* and *M. bovis*, the ordinary artisan would have been motivated to substitute amplification and hybridization of the DR region as taught by Kamerbeek and amplify the hupB gene specifically to include the 9 amino acid variation region to distinguish *M. tuberculosis* and *M. bovis*, as taught by Kamerbeek. From the teachings of the prior art, the ordinary artisan would have been taught that *M. tuberculosis* and *M. bovis* could be differentiated by amplification of DNA that varies in length between the two species and detection could be performed by hybridization of a probe to detect the amplicons. Therefore the ordinary artisan would have been motivated to use additional regions of DNA that vary between *M. tuberculosis* and *M. bovis*, including hupB, as taught by Furugen and it would have been *prima facie* obvious to the ordinary artisan at the time the invention was made to improve the method of Kamerbeek to include amplification of the hupB, specifically the region that comprises the 9 amino acid insertion as taught by Furugen, thus the generating multiple different size amplicons including a minimal length of 27 nucleotides. Furthermore, to practice the method, the ordinary artisan would have been motivated to generate a number of different primers and probes for use in the method including SEQ ID NO. 1 and 2 and hybridization probe SEQ ID NO. 7.

Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers, see Hogan et al. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers

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drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested new primers or probes to obtain additional oligonucleotides that function to differentiate *M. bovis* and *M. tuberculosis* by amplification of the *hupB* gene and identify oligonucleotides with improved properties. The ordinary artisan would have a reasonable expectation of success of obtaining additional probes from for the region of the *hupB* gene to include the 9 amino acid insertion in *M. tuberculosis* provided by Furugen. Thus, for the reasons provided above, the ordinary artisan would have designed additional probes, including labeled probes and varying sized amplicons using the teachings in the art at the time the invention was made.

11. Claims 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamerbeek et al. in view of Furugen, Hogan et al. and Buck et al as applied to claims 26-28, 31-41 above, and further in view of Taylor (J. Clin. Microbiol. 1997, vol. 35, pp. 79-.85) and Cuende et al. (Med Clin (Barc) 1995, vol. 104, pp. 207-10 (article in spanish), abstract only).

The method of Kamerbeek in view of Furugen, Hogan, and Buck is set forth in section 10 above. Kamerbeek in view of Furugen, Hogan, and Buck does not teach restricting the amplified fragment with *HpaII*, separating the restricted fragments by electrophoreses, and detecting the restricted fragments, nor teach lengths of 280 and 150bp or 253 and 150bp.

Taylor teaches PCR-restriction fragment length polymorphism to identify 28 species of clinically encountered mycobacteria for identification. Taylor teaches digestion of amplified

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products using Bst EII and HaeII followed by separation by gel electrophoresis and identified by staining with ethidium bromide (see pg. 80, 2nd column and figure 2).

Cuende et al. teaches amplification followed by RFLP analysis using HpaII and analysis on gel electrophoresis to generate 13 different patterns to type clinical isolates of mycobacteria (see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Kamerbeek in view of Furugen, Hogan, and Buck to include a step of RFLP analysis including digestion with HpaII followed by analysis by electrophoresis and ethidium bromide staining as Taylor teaches that PCR-RFLP is a rapid identification procedure of mycobacteria species. The ordinary artisan would have been motivated to improve the method of Kamerbeek in view of Furugen, Hogan, and Buck to include HpaII analysis and visualization by gel electrophoresis because Taylor teaches the PCR-RFLP method is a reliable technique that has the ability to identify rapidly mycobacteria and is easy to incorporate into the routine work flow of a microbiology laboratory (see pg. 84, last para) additionally, the ordinary artisan would have been motivated to include additional routine restriction enzyme, including HpaII and routine electrophoresis of nucleic acids, including 12% polyacrylamide gel, to thereby optimize experimental conditions and maximize experimental results. In performing the method of Kamerbeek in view of Furugen, Hogan, and Buck and further in view of Taylor and Cuende the ordinary artisan would have generated additional fragment lengths, including 280 bp, 150bp, 253 bp, and 150bp for analysis. It is noted that *In re Aller*, 220 F. 2d 454, 456, 105 USQ 233,235 states where the general conditions of the claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Conclusion

12. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Sarae Bausch/
Primary Examiner, Art Unit 1634

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